The Importance of Critically Analyzing Assumptions in Pharmacoeconomic Models: A Case Study in Modeling a Comparison of Diabetes Treatments

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MEDICAL DECISION MODELING

Background

- On June 30, 2014, the *Journal of the American Medical Association Internal Medicine* (*JAMA Internal Medicine*) published online "Effect of Patients' Risks and Preferences on Health Gains With Plasma Glucose Level Lowering in Type 2 Diabetes Mellitus" by Vijan et al.[1]
- Article conclusion was thought provoking and potentially clinical-practice changing[2]:

"***for most patients older than 50 years with an HbA1c level less than 9% receiving metformin therapy, additional glycemic treatment usually offers at most modest benefits.***"

1. Vijan et al. JAMA Intern Med. 2014 Aug;174(8):1227-34.
2. *JAMA Internal Medicine* is a highly influential journal, impact factor of 16.54, ranking 2nd among internal medicine journals, 6th among 156 general medical journals (https://jamanetwork.com/journals/jamainternalmedicine/pages/for-authors/)

Background

- Vijan et al. estimated the effects of hemoglobin A1c (HbA1c) reduction on diabetes clinical outcomes and overall quality-adjusted life years (QALYs) using a Markov simulation model
- Performed an intensive examination of the Vijan model, resulted in a number of questions related to assumptions, questions that could not be answered from the information provided in the article, its supplemental material, or the cited publications
- Assumptions in question greatly influence the results and subsequent conclusions, and thus merit greater transparency

Background

- Vijan et al. model compared two interventions:
  - “Initiation of metformin therapy at diagnosis”
  - “Switch to insulin” scenario, the patients’ HbA1c levels were assumed to have increased to 8.5% (presumably from 7.0%) over ten years

Background

- Serious questions about assumptions underlying modeling of each intervention
  - "Initiation of metformin therapy at diagnosis"
    - Model did not account for possibility of metformin failure
    - Patients not taking basal-bolus insulin have a demonstrated HbA1c drift over time, shown in multiple studies.[3,4,5,6,7]

3. Hollander et al. Diabetes Obes Metab. 2011 Mar;13(3):268-75.

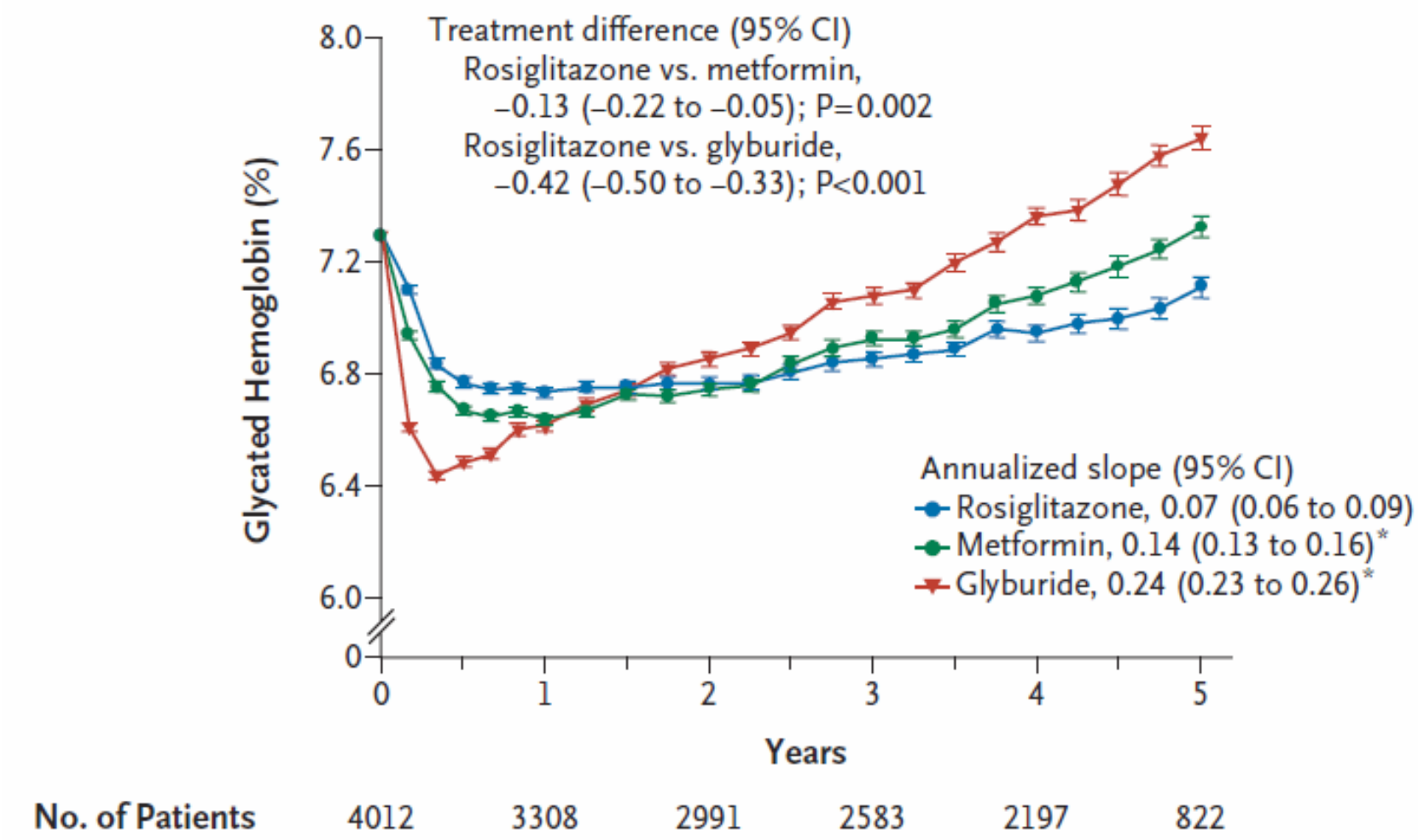
4. Diamant et al. Diabetes Care. 2012 Apr;35(4):683-9.

5. Hermansen et al. Diabetes Obes Metab. 2007 Sep;9(5):733-45.

6. Russell-Jones et al. Diabetologia. 2009 Oct;52(10):2046-55.

7. Schernthaner et al. Diabetes Care. 2013 Sep;36(9):2508-15.

Background – Metformin HbA1c drift



Kahn et al. N Engl J Med. 2006 Dec 7;355(23):2427-43

Background

- Serious questions about assumptions underlying modeling of each intervention
  - "Switch to insulin"
    - Patients' HbA1c levels were assumed to have increased to 8.5% (presumably from 7.0%) over ten years
    - Delay in treatment and time spent in poor glycemic control is a critically important determinant of patient outcomes[8]
    - Ten-year period of uncontrolled HbA1c levels increase the patients' risks of diabetes complications
      - Disutility from these increased complications incorrectly attributed by the model to the "insulin" scenario when in fact these are due to the failure of metformin to sustain glycemic control

8. Stratton et al. BMJ. 2000 Aug 12;321(7258):405-12.

Objective

- To examine the clinical and humanistic effects of incorporating HbA1c drift in a type 2 diabetes pharmacoeconomic model

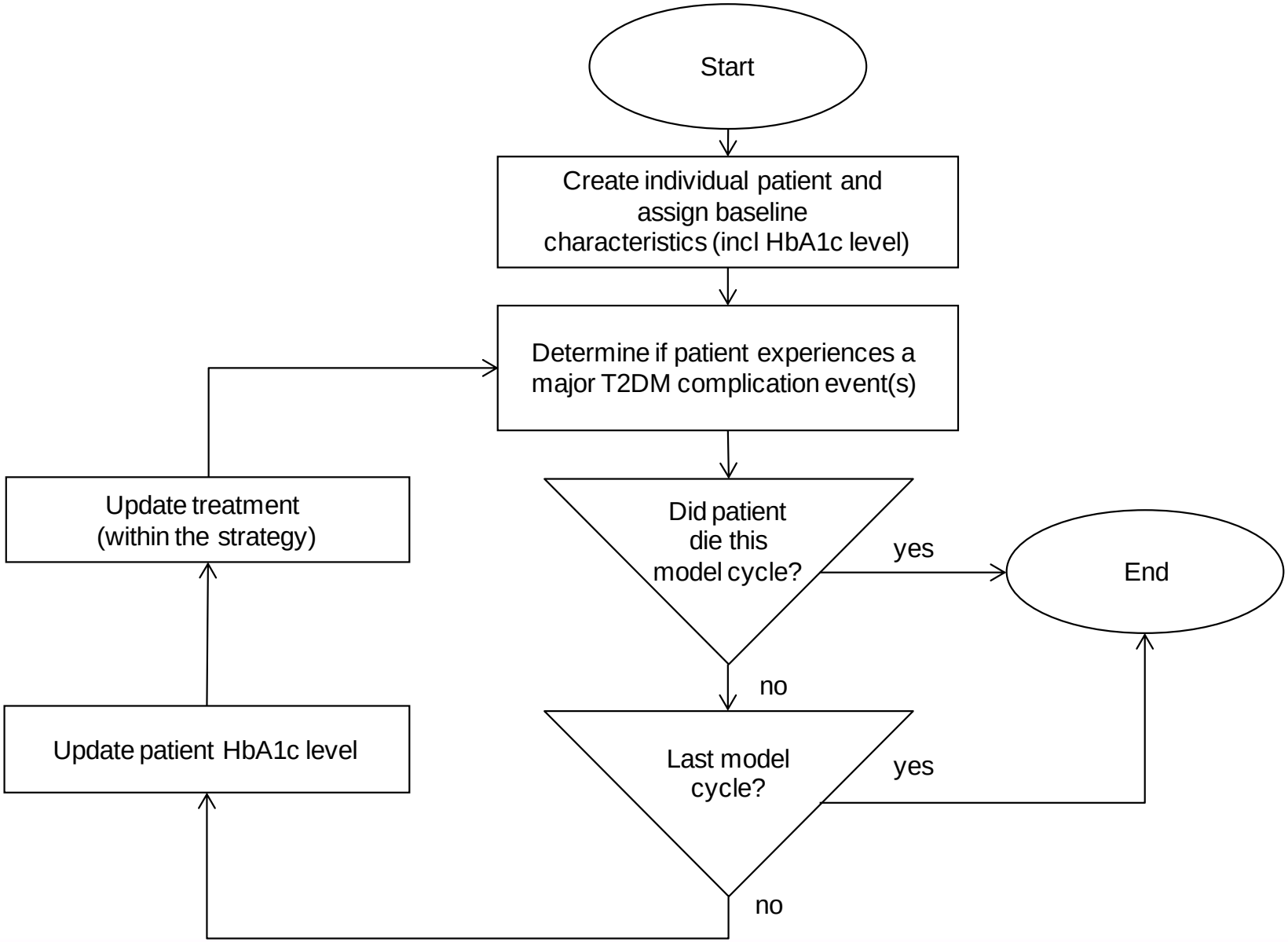
Methods

- Monte Carlo microsimulation model to estimate diabetes-related complications and mortality under various treatment strategies for newly-diagnosed patients with Type 2 diabetes mellitus (T2DM)
- Model is referred to as the Treatment Transitions Model (TTM)
- TTM is an adaptation of the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model 2, commonly referred to as "UKPDS 82"[9]

9. Hayes et al. Diabetologia. 2013 Sep;56(9):1925-33.

Methods

TTM Flow



Methods

- Underlying TTM are 17 multivariate regression equations estimating the probability of T2DM-related macrovascular and microvascular complications, and mortality
- Mean of 11 covariates per equation

Methods – Covariates

AGE DIAG – Age in years at diagnosis of diabetes	LDL>35 – Low density lipoprotein cholesterol (mmol/l)
CURR AGE – Current age in years	HEART R – Heart rate (beats per minute)
YEAR – Duration of diabetes (years)	eGFR – Estimated glomerular filtration rate
FEMALE – 1 for female; 0 for male	eGFR<60 – Estimated glomerular filtration rate
AFRO – 1 Afro-Caribbean ethnicity; 0 otherwise	eGFR>60 – Estimated glomerular filtration rate
INDIAN – 1 for Asian Indian ethnicity; 0 otherwise	MIC ALB – Presence of micro- or macro-albuminuria
SMOKER – 1 for current smoker; 0 otherwise	ATFIB – 1 for atrial fibrillation; 0 otherwise
BMI – Body mass index (m/kg^2)	PVD – 1 for peripheral vascular disease; 0 otherwise.
BMI CAT1 – Body mass index < $18.5 m/kg^2$	WBC – White blood cell count
BMI CAT3 – Body mass index > $25 m/kg^2$	HAEM – Haemoglobin g/dL
HbA1C – HbA1c (%)	AMP EVENT – 1 for first amputation; 0 otherwise
SBP – Systolic blood pressure (mm Hg)	AMP2 EVENT – 1 for second amputation; 0 otherwise
HDL – High density lipoprotein cholesterol (mmol/l)	AMP HIST – 1 for history of amputation; 0 otherwise
LDL – Low density lipoprotein cholesterol (mmol/l)	

Methods

Macrovascular complications, functional form of risk equation

- 1st congestive heart failure, Weibull
- 1st ischaemic heart disease, Weibull
- 1st myocardial infarction (male), Exponential
- 1st myocardial infarction (female), Weibull
- 2nd myocardial infarction, Exponential
- 1st stroke, Weibull
- 2nd stroke, Weibull

Methods

Microvascular complications, functional form of risk equation

- Blindness, Exponential
- Ulcer, Logistic
- 1st amputation no prior ulcer, Weibull
- 1st amputation no prior ulcer, Exponential
- 2nd amputation, Exponential
- Renal failure, Exponential

Methods

Microvascular complications, functional form of risk equation

- Death in years with no history or events, Gompertz
- Death in 1st year of event(s), Logistic
- Death in years with history but not events, Gompertz
- Death in subsequent year/s of event(s), Logistic

Methods – Example risk eq. calculation

Annual probability of congestive heart failure (CHF), functional form is Weibull

Baseline hazard

$$h_0(t) = \rho t^{\rho-1} \exp(\lambda)$$

Proportional hazards model

$$h(t|x_j) = h_0(t) exp(\beta_j x_j) = \rho t^{\rho-1} \exp(\lambda + \beta_j x_j)$$

Integrated hazard at time t

$$H(t|x_j) = \exp(\lambda + \beta_j x_j) t^{\rho}$$

Unconditional probability of CHF in the interval t to $t+1$

$$1 - \exp\{H(t|x_j) - H(t+1|x_j)\}$$

Methods – Example risk equation calculation

Calculation of probability of CHF in current year

Male, 70 years of age, 8-year history of diabetes, LDL 3.0 mmol/l, BMI of 32, eGFR 50, with microalbuminuria and a history of amputation

	Eq. 1
Complication	1st CHF
Patient-years	77941
Patients	4977
No of events	334
Functional form	Weibull

Parameters	Mean
λ	-12.332
ρ	1.514
AFRO	
AGE DIAG	0.068
FEMALE	
INDIAN	
ATFIB	~~1.562~~
BMI	0.072
eGFR	
eGFR<60	-0.220
HbA1C	
HDL	
LDL	0.012
LDL>35	
MMALB	0.771
PVD	~~0.479~~
SBP	
SMOKER	
WBC	
AMP HIST	0.658
CHF HIST	
IHD HIST	
STROKE HIST	
ULCER HIST	~~0.654~~

Methods – Example risk eq. calculation

t = 8 years of diabetes

$$H(t|x_j) = \exp(-12.332 + 0.068*62 + 3*10*0.012 + 0.072*32 + (50/10)*-0.22 + 0.771 + 0.658) * 8^{1.514}$$

$$= 0.1388$$

$t + 1$ = 9 years of diabetes

$$H(t+1|x_j))$$

$$= \exp(-12.332 + 0.068*62 + 3*10*0.012 + 0.072*32 + (50/10)*-0.22 + 0.771 + 0.658) * 9^{1.514}$$

$$= 0.1659$$

Probability of CHF in current year

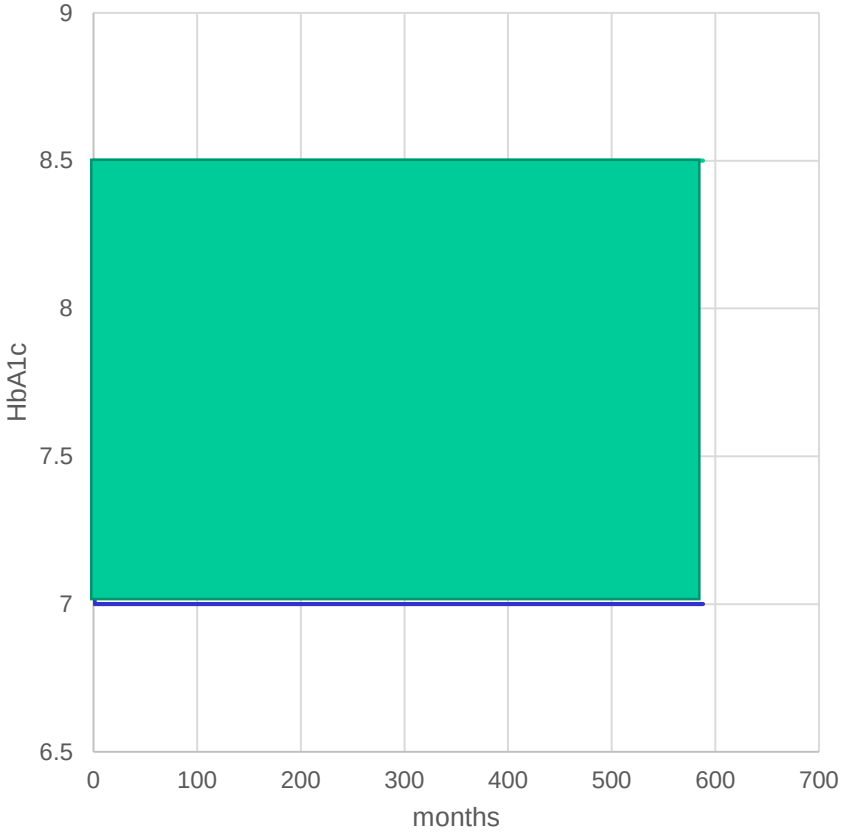
$$= 1 - \exp(0.1388 - 0.1659) = 0.027$$

Methods-scenario runs

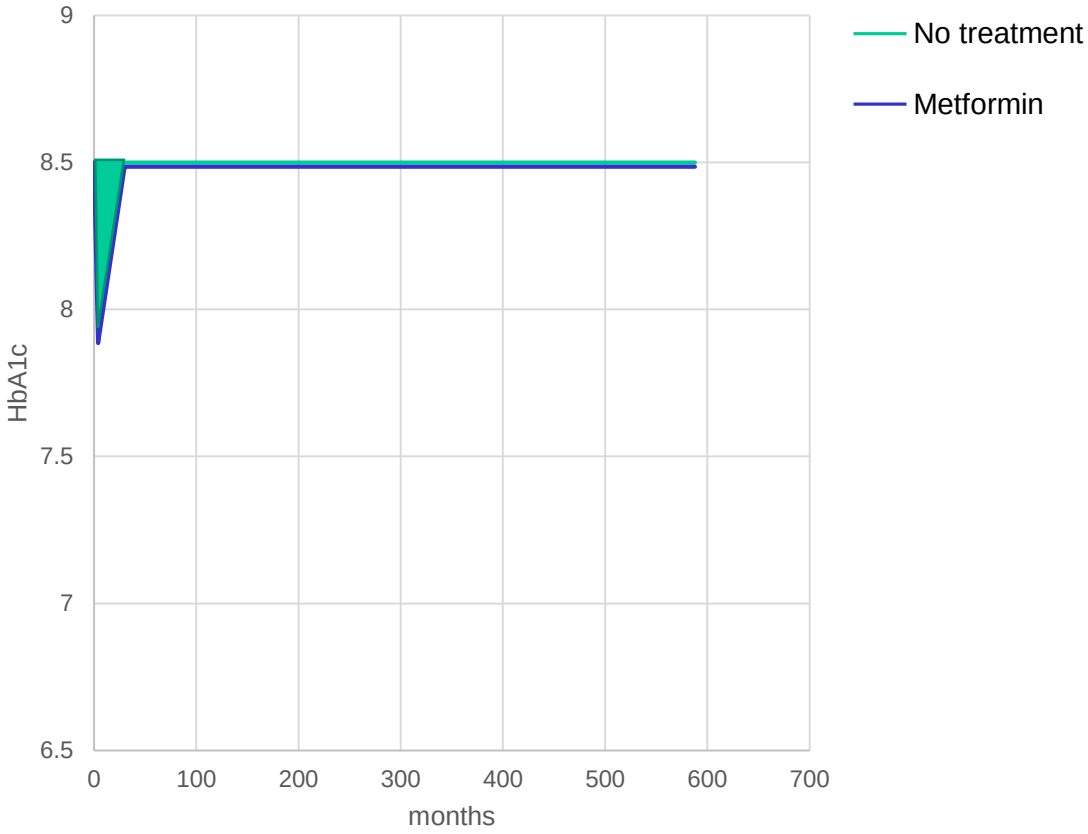
- T2DM patient baseline characteristics based on NHANES data: mean age 62, mean HbA1c 7.5
- Time frame: life time
- Base case: no treatment
- Comparator 1: metformin treatment without drift
- Comparator 2: metformin treatment with drift
- Comparator 3: insulin treatment
- Benefit of metformin treatment without drift, metformin treatment with drift and insulin treatment

Not considering drift according to Vijan et al.

Vijan metformin tx benefits:



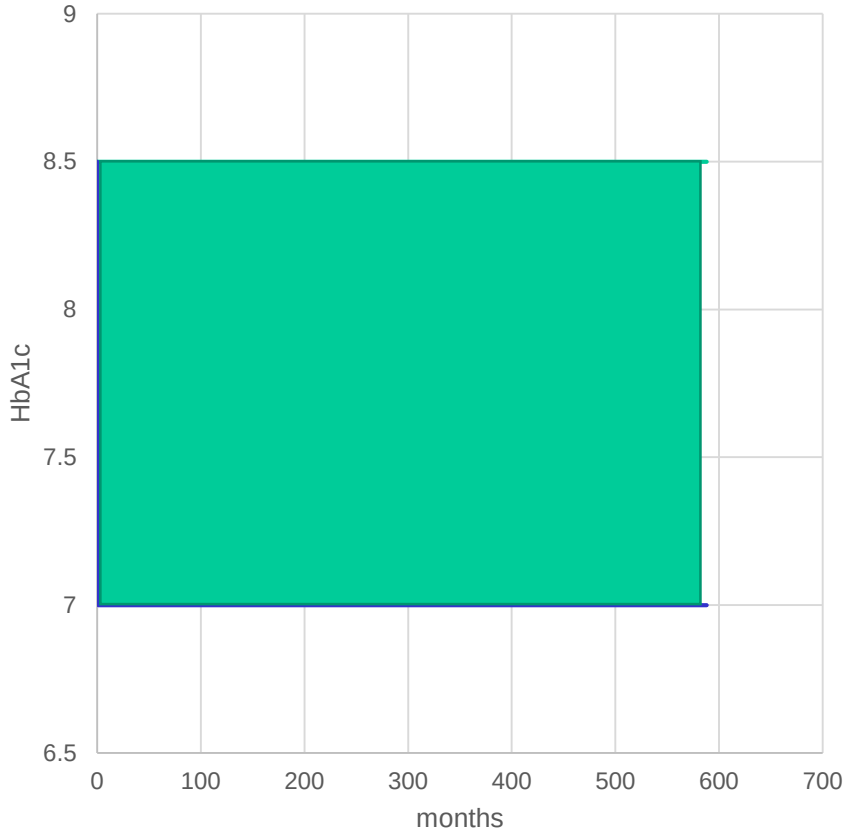
Real metformin tx benefits:



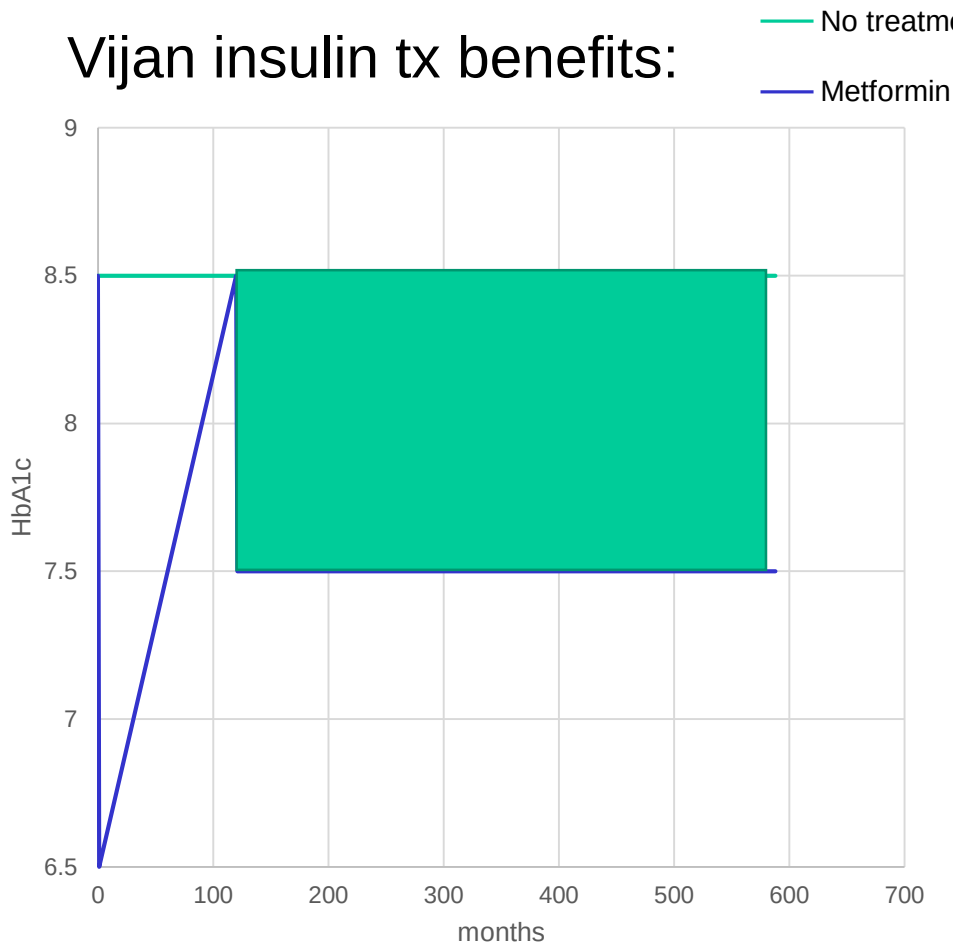
- Assume HbA1c keep constant when not on tx
- In reality/clinical trials: oral antidiabetic drugs suffer from HbA1c drift
- The benefit of metformin tx is overestimated when not considering drift

Not considering drift according to Vijan et al.

Vijan metformin tx benefits:

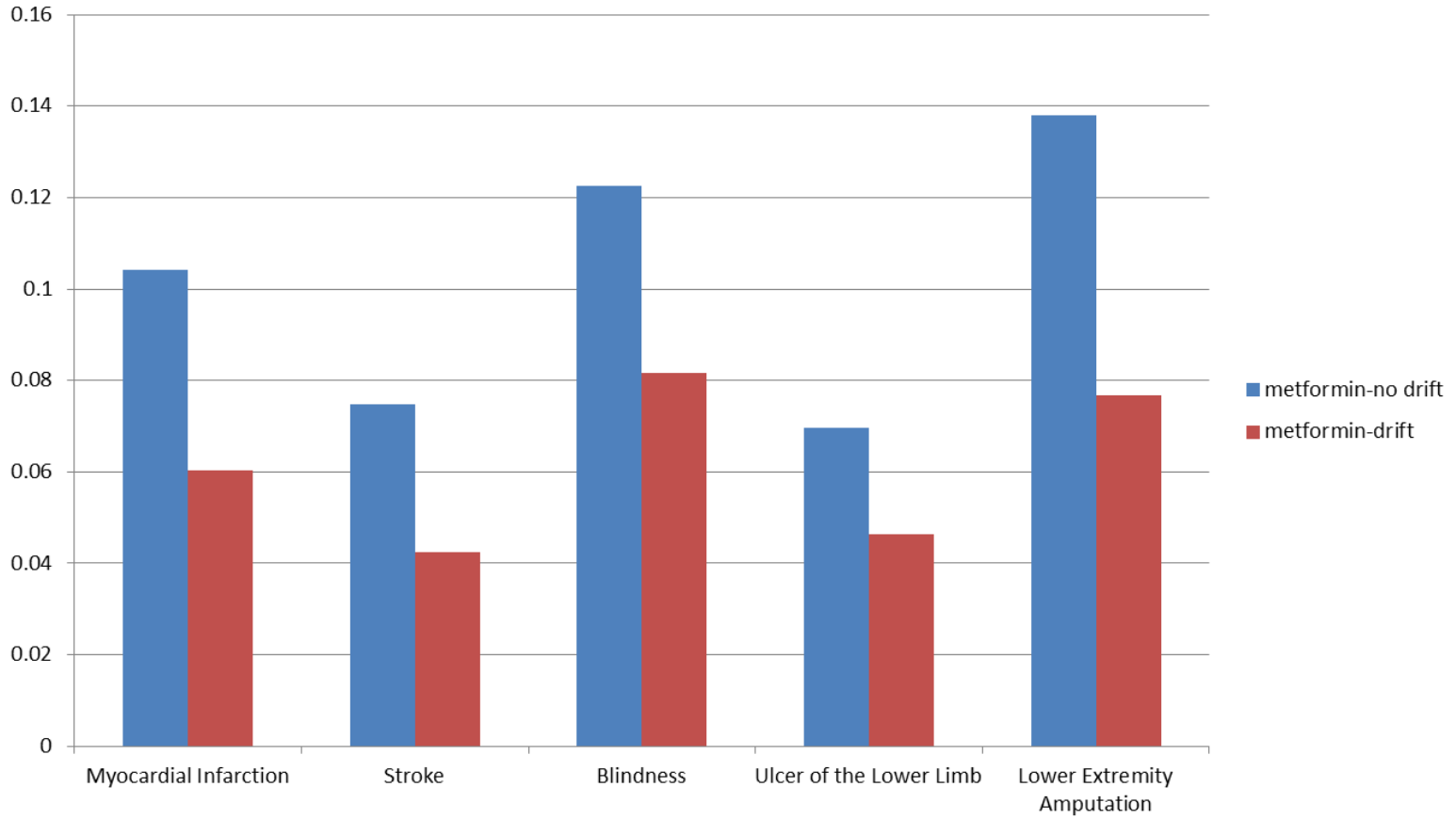


Vijan insulin tx benefits:



- False message delivered: metformin tx is way more beneficial than insulin tx

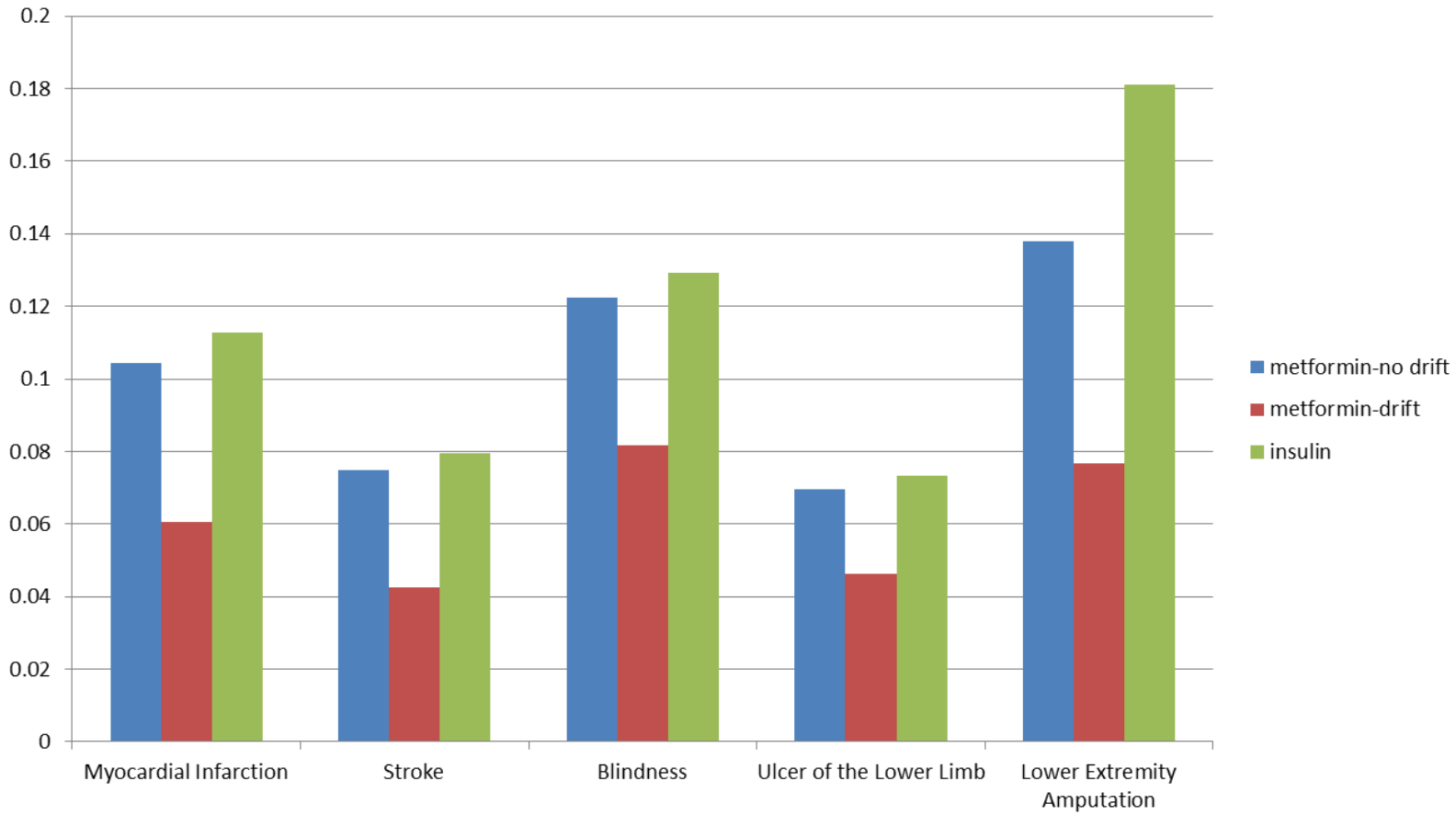
Results – Comparing benefit of metformin without and with drift



Complications prevented with metformin treatment

benefit of metformin (no drift) over no tx vs benefit of metformin (with drift) over no tx

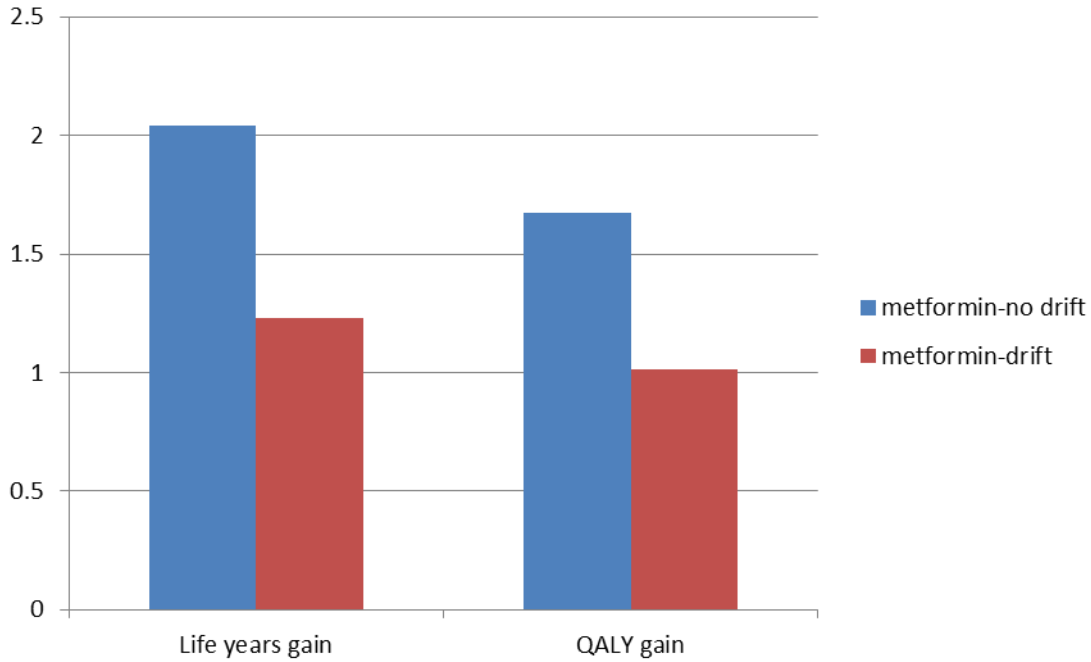
Results – Comparing benefit of metformin without drift, with drift, and insulin



Complications prevented with metformin or insulin treatment

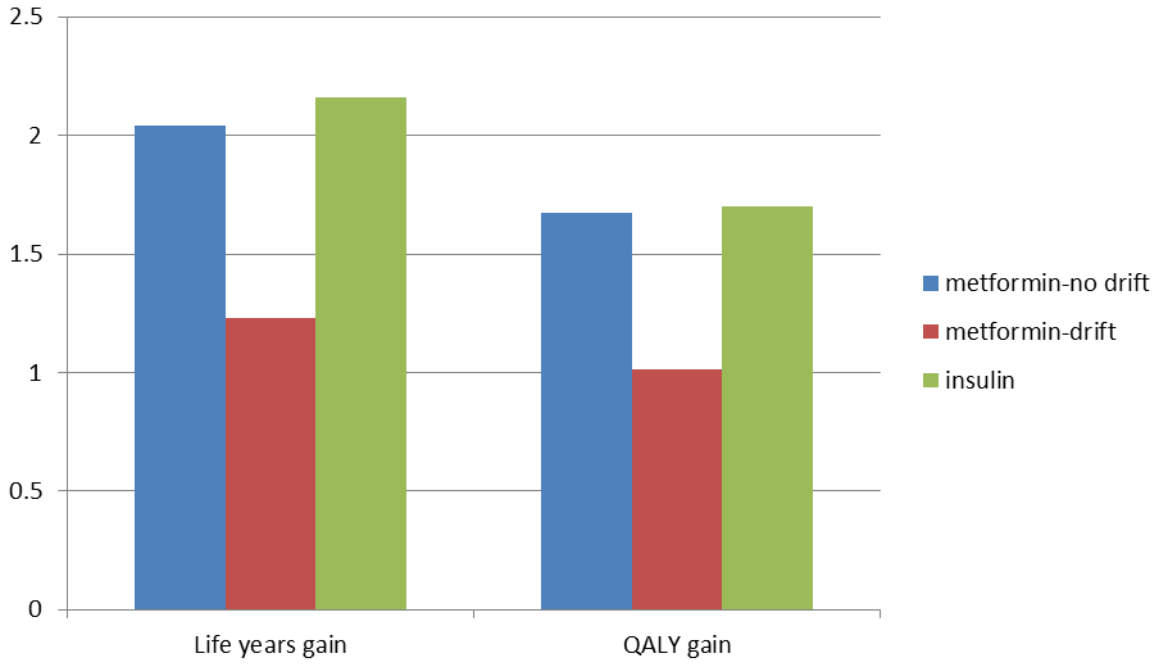
Benefit of insulin tx is larger than benefit of "real" metformin but is similar to benefit of the no-drift metformin

Results – Life years gain and QALY gain with metformin treatment



LY/QALY gain of metformin (no drift) over no tx vs LY/QALY gain of metformin (with drift) over no tx

Results – Life years gain and QALY gain with metformin or insulin treatment



- LY/QALY gain of insulin tx is larger than LY/QALY gain of “real” metformin but is similar to LY/QALY gain of the no-drift metformin

Conclusion

- Incorporating HbA1c drift, insulin is superior to metformin in:
  - Preventing myocardial infarctions, stroke, blindness, ulcers of the lower limb, and lower extremity amputation
  - Gaining life years and quality-adjusted life years (QALYs)
- Before accepting model conclusions, always investigate:
  - Fundamental model assumptions
  - Each treatment alternative assumptions